Citation:

Besser LM, Williams LJ, Cragan JD. Interpreting changes in the epidemiology of anencephaly and spina bifida following folic acid fortification of the US grain supply in the setting of long-term trends, Atlanta, Georgia, 1968-2003. *Birth Defects Res A Clin Mol Teratol*. 2007 Nov; 79(11): 730-736.

PubMed ID: 17990332

Study Design:

Trend Study

Class:

D - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To determine whether changes in the prevalence and characteristics of anencephaly (AN) and spina bifida (SB) in the years surrounding folic acid fortification could be distinguished from those resulting from pre-existing downward secular trends.

Inclusion Criteria:

Infants and fetuses with AN and SB delivered from January 1, 1968 through December 31, 2003.

Exclusion Criteria:

- Those with craniorrhachischisis, iniencephaly, lipomyelomeningocele, amniotic bands, diagnosed chromosomal abnormalities, clinical syndromes of known etiology and more than one neural tube defect present simultaneously (e.g., AN and SB, AN and encephalocele or SB and encephalocele in the same infant)
- Conjoined twins, acardiac twins and those for whom the diagnosis was uncertain based on the clinical description in the medical record.

Description of Study Protocol:

Recruitment

Data from the Metropolitan Atlanta Congenital Defects Program (MACDP) that identifies birth defects among infants and fetuses of at least 20 weeks gestation born to residents of the five central counties of metropolitan area in Atlanta, Georgia in the United States

Design

Cross-sectional study.

Intervention

To compare the prevalence of AN and SB across time and to whether there was a change in the prevalence based on several characteristics, including birth outcome, sex, race, gravidity or mother's age.

Statistical Analysis

Poisson regression (SAS version 9.0) and crude prevalence ratios and Mantel-Haenzel 95% confidence intervals.

Data Collection Summary:

Timing of Measurements

Three periods between January 1, 1968 and December 31, 2003:

- *1968 to 1981 (Period One):* When prenatal diagnosis was rarely used
- *1981 to 1993 (Period Two):* When the use of prenatal diagnosis was increasing in Atlanta but MACDP did not ascertain prenatal diagnoses from outpatient sources
- *1994 to 2003 (Period Three):* When prenatal diagnosis was used in Atlanta and MACDP ascertained prenatal diagnoses from outpatient sources and years during which folic acid fortification of enriched grains was implemented (authorized in March 1996; mandatory by January 1, 1998).

Dependent Variables

- Prevalence of AN and SB over time for three time periods: Plotted number of infants and fetuses with AN or SB per 10,000 live births and determined slope of line regression line using Poisson regression. The slope was defined as the annual percent change in AN or SB prevalence. The number of live births to residents of these same five counties during the same time period was determined from birth certificate data from the Division of Vital Records, Georgia Department of Human Resources
- Prevalence of AN and SB during each prenatal ascertainment period for the following: Pregnancy outcome, sex, mother’s race, gravidity and mother's age.

Independent Variables

- Pregnancy outcome (stillbirth, live birth, elective termination)
- Infant or fetal sex
- Mother’s race (African American or white: Prior to 1973, race was categorized on Georgia birth certificates as either white or other)
- Gravidity: Number of previous pregnancies (more than one, one or zero)
- Maternal age (less than 20, 20 to 29, greater than or equal to 30).

Description of Actual Data Sample:

- *Initial N:* 1,287 and 190 were excluded based on the exclusion criteria
- *Attrition:* 434 infants with AN and 663 infants with SB
- *Ethnicity:* White or African American
- *Anthropometrics:* Anthropometrics were reported; however, a statistical analysis was not completed to determine whether groups were similar or different
- *Location:* Five central counties of metropolitan Atlanta, Georgia in the United States.

Summary of Results:

There was a significant difference between the annual percent change for anencephaly between periods one and two.

Ascertainment Period	Anencephaly: Annual Percent Change (95% CI)	Spina Bifida: Annual Percent Change (95% CI)
Period One: 1968 to 1981	-6.9 (-10.9, -3.6)	-7.1 (-9.7, -4.5)
Period Two: 1982 to 1993	-2.9 (-7.9, 2.3)	-7.0 (-10.7, -3.0)
Period Three: 1994 to 2003	-6.8 (-12.6, -0.7)	-6.2 (-11.2, -0.9)

Anencephaly:

- Prevalence among stillbirths relative to live births decreased and prevalence among elective terminations increased. Authors suggests this reflects the increased use of prenatal diagnosis in Atlanta over time
- Prevalence among females relative to males decreased. Authors suggest a change in the sex ratio over time
- Prevalence among whites relative to blacks or African Americans decreased. Authors suggest a more rapid decline in AN among whites over time
- Prevalence across gravidity and mother's age across the time periods was constant.

Prevalence of Anencephaly by Clinical and Demographic Characteristics and Period of Prenatal Ascertainment, Metropolitan Atlanta, 1968 to 2003 Prevalence of Anencephaly by Clinical and Demographic Characteristics and Period of Prenatal Ascertainment, Metropolitan Atlanta, 1968 to 2003

Characteristic	Period One: (1968 to 1981)			Period Two: (1982 to 1993)			Period Three: (1994 to 2003)		
	N	Prev	PR (95% CI)	N	Prev	PR (95% CI)	N	Prev	PR (95% CI)
Total	199	5.5		119	2.9		116	2.5	
Outcome									
Live birth	70	1.9	Referent	45	1.1	Referent	25	0.5	Referent

Stillbirth	126	3.5	1.8 (1.4 to 2.4)	47	1.1	1.0 (0.7 to 1.6)	23	0.5	0.9 (0.5 to 1.6)
Elective Termination	<5	0.1	0.03 (0.01 to 0.1)	27	0.7	0.6 (0.4 to 1.0)	63	1.4	2.5 (1.6 to 4.0)
Sex									
Male	62	3.4	Referent	40	1.9	Referent	44	1.9	Referent
Female	135	7.7	2.3 (1.7 to 3.1)	73	3.6	1.9 (1.3 to 2.8)	52	2.3	1.2 (0.8 to 1.9)
Race									
White	167	7.0	2.7 (1.9 to 4.1)	73	3.0	1.3 (0.9 to 2.0)	54	2.2	1.2 (0.8 to 1.9)
Black or African American[a]	30	2.5	Referent	37	2.3	Referent	32	1.8	Referent
Other	<5	N/C		8	8.4	3.7 (1.6 to 7.5)	24	9.5	5.4 (3.1 to 9.5)
Gravidity									
0	77	4.8	Referent	33	2.3	Referent	30	1.9	Referent
1+	122	6.5	1.4 (1.0 to 1.8)	86	3.2	1.4 (0.9 to 2.1)	76	2.6	1.4 (0.9 to 2.1)
Mother's age (years)									
Less than 20	42	6.0	1.1 (0.8 to 1.6)	1.8	3.5	1.2 (0.7 to 1.9)	13	2.7	1.0 (0.5 to 1.8)
20 to 29	121	5.4	Referent	69	3.0	Referent	59	2.7	Referent
30 or more	35	5.4	1.0 (0.7 to 1.4)	32	2.5	0.8 (0.5 to 1.2)	43	2.2	0.8 (0.6 to 1.2)

[a] For 1968 to 1972, the number of births of "Other" race was used as the denominator for blacks or African Americans.
Prev, prevalence per 10,000 live births; PR, prevalence ratio; CI, confidence interval; N/C, prevalence not calculated.

Spina bifida (see table below):

- Prevalence among stillbirths relative to live births remained constant and prevalence among elective terminations increased over time
- Prevalence among females relative to males decreased
- Prevalence among whites relative to blacks or African Americans decreased. Author's suggest a more rapid decline in SB among whites over time.
- Prevalence across gravidity and mother's age across the time periods was constant.

Prevalence of Spina Bifida by Clinical and Demographic Characteristics and Period of Prenatal Ascertainment, Metropolitan Atlanta, 1968 to 2003

Characteristic	Period One: (1968 to 1983)			Period Two: (1982 to 1993)			Period Three: (1994 to 2003)		
	N	Prev	PR (95% CI)	N	Prev	PR (95% CI)	N	Prev	PR (95% CI)
Total	309	8.6		195	4.7		159	3.5	
Outcome									
Live birth	273	8.6	Referent	167	4.0	Referent	87	1.9	Referent
Stillbirth	34	7.6	0.1 (0.1 to 0.2)	15	0.4	0.1 (0.95 to 0.2)	9	0.2	0.1 (0.05 to 0.2)
Elective termination	<5	0.9	0.01 (0.001 to 0.02)	13	0.3	0.1 (0.04 to 0.1)	55	1.2	0.6 (0.5 to 0.9)
Sex									
Male	150	8.1	Referent	97	4.6	Referent	80	3.4	Referent
Female	157	8.9	1.1 (0.9 to 1.4)	96	4.8	1.0 (0.8 to 1.4)	65	2.9	0.8 (0.6 to 1.2)
Race									
White	256	10.7	2.5 (1.8 to 3.4)	133	5.5	1.6 (1.2 to 2.3)	74	3.0	1.1 (0.8 to 1.6)
Black or African American[a]	51	4.3	Referent	54	3.4	Referent	49	2.7	Referent
Other	<5	N/C		8	8.4	2.5 (1.1 to 5.0)	27	10.7	4.0 (2.5 to 6.3)
Gravidity									
0	101	6.3	Referent	59	4.1	Referent	33	2.1	Referent
1+	201	10.8	1.7 (1.3 to 2.2)	136	5.1	1.2 (0.9 to 1.7)	109	3.7	1.8 (1.2 to 2.7)
Mother's age (years)									
<20	48	6.9	0.8 (0.6 to 1.1)	23	4.4	0.9 (0.5 to 1.3)	18	3.8	1.1 (0.6 to 1.8)
20 to 29	193	8.6	Referent	118	5.1	Referent	76	3.5	Referent
30 or more	63	9.6	1.1 (0.8 to 1.5)	54	4.2	0.8 (0.6 to 1.1)	65	3.4	1.0 (0.7 to 1.4)

[a] For 1968 to 1972, the number of births of "Other" race was used as the denominator for blacks or African Americans.
Prev, prevalence per 10,000 live births; PR, prevalence ratio; CI, confidence interval; N/C, prevalence not calculated.

Author Conclusion:

- The study demonstrated the difficulty in assessing the effect of an intervention such as folic acid fortification of enriched grains in the context of such pre-existing trends
- Birth defects programs should consider this when using surveillance data to evaluate the success of prevention efforts
- This also emphasizes the critical need for the larger sample sizes available through the combination of high-quality, population-based, state-level birth defects surveillance data.

Reviewer Comments:

- *As stated by the authors: "Prior to 1973, race was categorized on Georgia birth certificates as either white or other. Because the Atlanta population comprised mostly whites and blacks or African Americans during this time, the number of live births of other race was used as the denominator for black or African American race."*
- *Limitations stated by the authors:*
  - *Progressively smaller number of AN and SB cases over time may have limited the ability to identify changes in AN and SB prevalence*
  - *Development of prenatal diagnostic technology over the course of the study period and changes in ascertainment of these diagnoses by MACDP over time: MACDP began ongoing ascertainment of prenatal diagnoses from outpatient settings only two years before folic acid fortification of enriched grain products was authorized. Trends in AN and SB prevalence may not have been tracked consistently over time*
  - *Change in demographic characteristics of the Atlanta population over time: Reduction of number of mothers of live births classified as white decreased from 72% in 1968 to 1972 to 38% in 1999 to 2003*
  - *Mother's age increased: Mothers of live births who were 30 years of age or older increased from 16% in 1968 to 1972 to 42% in the third time period*
  - *MACDP surveillance data do not include information about peri-conceptional folic acid intake or use of multivitamins.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	No
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	No
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	No
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	No
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	N/A

4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	No
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	No
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes

7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	???
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	No
10.2.	Was the study free from apparent conflict of interest?	Yes